EXHIBIT 18

Inhalation Drug Products in LDPE Containers: A Quality (CMC) Perspective

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Outline

- Inhalation Drug Products
- Container-Closure System Overview
- FDA Analytical Survey and Other Data
- Quality Concerns
- Potential Approaches
- Recommendations for Packaging
- Summary

Inhalation Drug Products

- **Inhalation Solution**
- **Inhalation Suspension**
- Inhalation Spray
  - Solution
  - Suspension
- Inhalation Aerosol (Metered Dose Inhaler)
  - Solution
  - Suspension
- Inhalation Powder (Drug Powder Inhaler)

Drug Product Examples

- Albuterol SO_4 Inhalation Solution
- Levalbuterol HCl Inhalation Solution
- Ipratropium Br Inhalation Solution
- Albuterol SO_4 and Ipratropium Br Inhalation Solution
- Metaproterenol SO_4 Inhalation Solution
- Cromolyn Na Inhalation Solution
- Budesonide Inhalation Suspension
- Tobramycin Inhalation Solution

Current Container-Closure System

Inhalation Solution and Suspensions:

- Unit-Dose containers/Vials (UDV)
  - LDPE vials
  - Blow-Fill-Seal/Form-Fill-Seal Process
- Vial label
  - Emboss, Deboss
  - Self-adhesive Paper label
- Foil overwrap pouch (1, 4, 5, 12 vials/pouch)
  - Pre-printed
  - Self-adhesive Paper label

Container-Closure Components

LDPE vial

LDPE Characteristics

- Low density polyethylene (LDPE) is a polyethylene homo-polymer resin:

$$-[-CH_2-CH_2-]_n-$$

- Resin Components:
  - Reactant monomer, Chain transfer agent, Chain initiator, Antioxidant, Stabilizers, Slip Additive, Superfloss Antiblock additive
- Different grades for different applications
- Many sources: Manufacturers, suppliers

LDPE Vial Properties

- Flexible and malleable
- Stress crack, impact and tear resistant
- Considered chemically inert at room temperature
- May be usable up to 80°C for extended periods
- Sterilizable
- Amenable to high speed production lines
- Aesthetically, clear to translucent to opaque

- **Permeable** to volatile chemicals and gases

Container-Closure Components

Paper label

Typical Paper label Components

- Calcium Carbonate
- Kaolin Clay
- Ethylated Corn Starch
- Cationic Potato Starch
- Sodium Bicarbonate
- AKD
- Colloidal Silica
- Liquid Alum
- Latex Calcium
- Stearate
- Viscosity Modifier
- Polyvinyl Alcohol
- Ammonium Zirconium Carbonate
- Carboxymethylcellulose
- Dispersant
- Microbiocide
- Fluorescent Dye
- Pigment Dye

Typical Adhesive Components

- Aromatic C5 hydrocarbon resin
- Polymeric hindered phenol (Anti-oxidant)
- Diastearyl pentaerythrotol diphosphate (Anti-oxidant)
- Styrene-isoprene-styrene block polymer,
- Naphthenic Oil
- Liquid C5 hydrocarbon resin

Typical Over-lacquer Components

- Joncryl 60, 89, 624
- Wax dispersions (e.g., Liquitron 345)
- Defomers (e.g., Tego Foamex 1488)
- Non silicone Defomers (e.g., Nopco NDW)
- Grease resistant coating Agents (e.g., Scotchban FC-807)
- PTFE Dispersions (e.g., Fluotron 300)
- Slip Additives (e.g., Dow 51 Additive
- Lucidene 614
- Morcryl 360
- Surfactants (e.g., Aerosol OT-75)
- Syloid silicas
- Methyl-n-2-pyrrolidone
- Aqua Ammonia
- Normal propanol
- Water

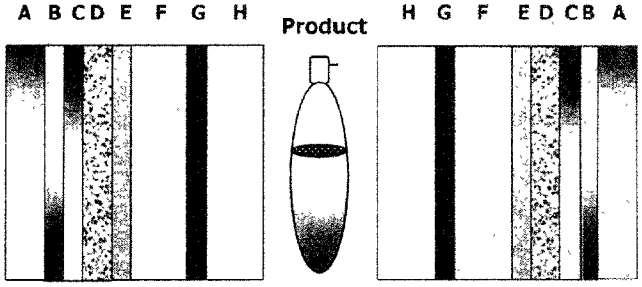
Typical Ink Components

- Acrylic resin
- Styrene acrylic polymers
- Surfactant
- Cellulosic defoamer
- Maleic resin chip
- Pigment Dyes:
  - Carbazole violet 23
  - Phthalocyanine blue
  - Phthalocyanine green 7
- Pigment Dyes:
  - Red 238
  - Violet 23
  - Black 7
  - Yellow 74
  - Green 7
  - Blue 15
  - Red 57
  - Violet 3

Container-Closure Components

Foil-laminate

Typical Foil-laminate Components



A = Exterior layer Polyester/PP/PE (0.00048 inch)
B = Inks
C = Adhesive1

D = Aluminum Foil (0.00035 inch)

E = Adhesive2
F = Nylon/Polyester/PP/PE(0.001 inch)
G = Adhesive3
H = Interior layer Polyester/PP/PE (0.003 inch)

LDPE Vial Permeability: Implications

- Contamination of drug product with ingress of volatile chemicals from the environment that may be irritants or toxic to the respiratory tract, and may sensitize individuals.
- Degradation of the drug products in LDPE vials by reactive gases and light.
- Water evaporation through LDPE vials, altering the concentration of drug product in LDPE vials.
- Potential acceleration of drug product degradation (impurities) due to change in drug concentration.

FDA Analytical Survey and Other Supportive Data

FDA Analytical Survey

- Initiated by OGD & DPADP/OND in coordination with OC/ORA Field Offices and Pacific Regional Laboratory.
- 7 ANDAs and 1 NDA for Inhalation solutions covering five different drug substances.
  - 38 samples representing 37 Lots of various drug products in LDPE vials without a protective overwrap foil-pouch.
  - Samples screened for potential volatile chemicals such as *vanillin, 2-phenoxyethanol, and 1-phenoxy-2-propanol* by GC-MS (sensitivity ~ 0.5 ppm) and HPLC methods.

FDA Analytical Survey: Results

- **29** out of **38** samples tested positive for chemical contamination originating from packaging.
- Detected **5** known chemical contaminants originating from packaging.
  - *Benzophenone (2 lots)*
  - *Polyethylene glycols (n = 4 -8), (3 lots)*
  - *2-(2-Butoxyethoxy)ethanol (DEGBE), (24 lots)*
  - *2-(2-Ethoxyethoxy)ethanol acetate (DEGEEA), (3 lots)*
  - *2-Hydroxy-2-methylpropiophenone (2-HMPP), (5 lots)*

FDA Analytical Survey: Conclusion

- Potential for these chemicals to cause bronchospasm at levels detected is unknown, especially, in patients with respiratory diseases.
- Concentration of these chemicals might be greater at the end of expiry than what was detected.
- Ingress/Leaching of chemical contaminants into drug product formulations from packaging components demonstrates that **permeation** through LDPE is a real phenomenon.
- Additional chemicals may be present, but may not get detected by the analytical procedures used.
- Future changes in the materials used in labeling and packaging may result in contamination with different chemicals.

Typical Sources of Product Contamination

- **Formulation components (Degradation)**
  - Drug substance, excipients, formulation vehicle
- **Resin components (Leaching)**
  - Monomer, dimer, antioxidants, plasticizers, catalysts etc.,
- **Paper label components (Leaching)**
  - Paper, adhesive, varnish/over lacquer, inks, residual volatile solvents
- **Foil overwrap components (Leaching)**
  - Adhesive, residual volatile solvents
- **Cartons (Leaching)**
  - Adhesive, residual volatile solvents
- **Environment (Leaching)**
  - Reactive gases, volatile pollutants

Extractable/Leachable: Examples

- **Resin components**
  - Irganox 129, 2, 2, 6-trimethyloctane
- **Paper label components**
  - Benzoic acid, ethyl phthalate, benzophenone, Danocur 1173, cyclic phthalates
- **Foil overwrap components (Leaching)**
  - Methacrylic acid, 2-phenoxyethanol
  - Acetone, 2-butanone, ethylacetate, propylacetate, heptane, toluene
- **Cartons (Leaching)**
  - Methacrylic acid, 1-phenoxy-2-propanol

Quality Concerns

- Proprietary components and composition of packaging materials.
- Change in the components and composition of these materials without the knowledge of applicant and the Agency.
- No one analytical procedure to detect known/unknown chemical contaminants.
- Incomplete toxicological data for many of the identified chemical contaminants.
- Variable environmental conditions may introduce new contaminants.

Potential Approaches

Agency's Quality Control Approach

- Characterize/Identify all possible *extractables* and establish a profile for each packaging component (e.g., resin, vial, paper label, foil-laminate overwrap).
- Establish a correlation between *extractable* and its *leachable* potential.
- Set meaningful acceptance criterion for a given *extractable* in corresponding incoming packaging components, based on its qualification level and actual observed data.
- Set meaningful acceptance criterion for a given *leachable* based on actual observed data in the drug product.

Extractable & Extractable Profile

- **Extractable** is a chemical compound (volatile, non-volatile) that gets extracted from a packaging component in a suitable solvent by utilizing optimum extraction conditions (time and temperature).
- Extractable profile for a given packaging component, typically can be a chromatogram (GC, HPLC, GC-MS, LC-MS) representing all possible extractables.
- Extractable profile is established for all packaging components (resin, vial, foil-laminate) for their consistent quality assurance.

Leachable

- **Leachable** is any chemical compound (volatile, non-volatile) that leaches into the drug product formulation either from a packaging component or local environment on storage (time and temperature) through expiry of the drug product. An extractable can be a leachable.
- To ensure batch-to-batch consistency of the drug product, appropriate specification (test method, acceptance criteria) for a leachable is established based on its qualification (toxicity) and observed levels in the drug product on storage.

Recommendations

Recommendations

- Adequate knowledge of composition and physico-chemical properties of packaging components for appropriate selection.
  - Resin components, foil-laminate, paper label, inks (aqueous vs. non-aqueous base), etc.
- Discourage paper label directly on the LDPE vial.
- Encourage alternative approaches, including embossing/debossing in lieu of the paper label on the LDPE Vial.
  - Extended bottom flanges to UDV to carry essential vial labeling information and product identity.

Recommendations

- Use of protective overwrap foil-pouch for the LDPE unit-dose vial (UDV)
  - Can minimize ingress and leaching of chemical contaminants from the local environment.
- Self-adhesive paper label on a foil-pouch or pre-printed foil-pouch and different color schemes to differentiate multiple strengths of the drug product.
  - Prevent ingress/leaching of chemical contaminants from paper labels and also improve the legibility issues.

Recommendations

- Limit the number of unit-dose-vials per pouch, ideally to one LDPE vial per foil-pouch.
  - Minimize the risk of medication error by patients and health care professionals
  - Prevent unnecessary exposure to local environment (When compared to packaging of multi UDVs/Foil-pouch)

Summary

- Volatile chemicals present in the packaging components and local environment have great potential to permeate through LDPE vials into drug product formulation on storage (time and temperature).
- Agency's Analytical Survey and other supportive data have confirmed ingress/leaching of such volatile chemicals into the drug product formulations.

Summary

- Ingress/leaching of such chemicals into drug product formulation poses a safety concern for patients with respiratory illness (Asthma, COPD).
- Embossing/debossing of LDPE vial in lieu of paper label is recognized to have legibility issue.
- Paper labels, although perceived to address legibility issue, overall may not be the **optimum** solution because of the safety concerns associated with potential leaching/ingress of paper label components in the drug product through LDPE vial.

Summary

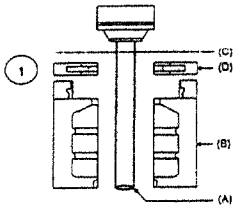
- Agency's current recommendations as stated in the draft guidance may serve as a first step in right direction to address the issues that are being discussed today.
- Agency is seeking other viable approaches to address these issues to promote safe product use without compromising the integrity of the drug product.

Inhalation Drug Products in LDPE Containers: A Quality Perspective

Thanks.

Blow-Fill-Seal (BFS) a.k.a Form-Fill-Seal (FFS) Process

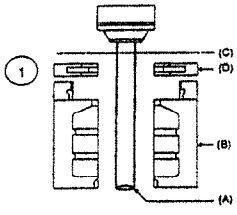
Blow-Fill-Seal / Form-Fill-Seal Processes



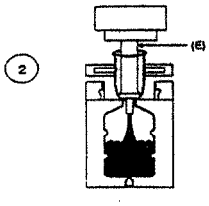
Extrusion

- Thermoplastic resin beads are pneumatically fed into the B/F/S machine. The beads enter an extruder where they are melted by heat generated by electric band heaters and physical compression.
- The molten thermoplastic is then continuously extruded through an orifice in a tubular shape [parison, (A)].
- The machine simultaneously extrudes six parisons per machine cycle and forms/fills four vials per parison. Filtered ballooning air continuously passes through the formed parison to maintain its shape.

Blow-Fill-Seal / Form-Fill-Seal Processes

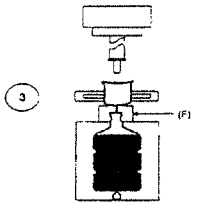


Blow & Fill

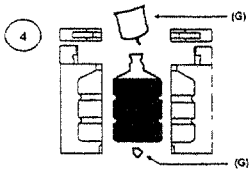


- When the tube (parison) reaches the proper length, the main mold (B) closes and the parison is cut off at (C).
- The bottom of the parison is pinched closed and the top is held open by a set of holding jaws (D).
- Vacuum ports in the mold cavity walls activate to form the container. The mold then moves to a position under the filling nozzle.
- The filling nozzle (E) lowers Into the parison unit it forms a seal with the neck of the mold.
- A metered amount of product is then transferred Into the container.

Blow-Fill-Seal / Form-Fill-Seal Processes



Seal



- **When the container is filled, the filling nozzle retracts to its original position.**
- **At this point in the cycle, the length of parison between the top of the mold and the holding jaws is still semi-molten.**
- **A sealing mold (F) doses to form the top and hermetically seal the container.**
- **Once the container is sealed, the sealing mold, main mold, and holding jaws open. A trim die removes residual plastic (G) and a formed, filled, and sealed container is conveyed out of the machine.**

Drug Product Examples

- Albuterol SO_4 Inhalation Solution (AccuNeb®, Proventil®, Ventolin®)
- Levalbuterol HCl Inhalation Solution (Xopenex®)
- Ipratropium Br Inhalation Solution (Atrovent®)
- Albuterol SO_4/Ipratropium Br Inhalation Solution (DuoNeb®)
- Metaproterenol SO_4 Inhalation Solution (Alupent®)
- Cromolyn Na Inhalation Solution (Intal®)
- Budesonide Inhalation Suspension (Pulmicort®)
- Tobramycin Inhalation Solution (Tobi®)